

FILE 'HCAPLUS' ENTERED AT 14:54:30 ON 28 APR 2009  
L1 31321 S HERPES OR HSV OR HSV1 OR HSV2  
L2 1224 S ((ACYCLOVIR OR GANCYCLOVIR OR NUCLEOSIDE) (W) (PHOSPHATE OR PHO  
L3 102 S L1 AND L2  
L4 72 S L3 AND (PY<2003 OR AY<2003 OR PRY<2003)

FILE 'STNGUIDE' ENTERED AT 14:54:36 ON 28 APR 2009

FILE 'HCAPLUS' ENTERED AT 14:55:16 ON 28 APR 2009  
L5 10514 S THYMIDINE KINASE  
L6 11 S L4 AND L5

=> file hcplus  
COST IN U.S. DOLLARS  
FULL ESTIMATED COST

SINCE FILE  
ENTRY  
0.88  
TOTAL  
SESSION  
0.88

FILE 'HCPLUS' ENTERED AT 14:54:30 ON 28 APR 2009  
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FILE COVERS 1907 - 28 Apr 2009 VOL 150 ISS 18  
FILE LAST UPDATED: 27 Apr 2009 (20090427/ED)

HCPlus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

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<http://www.cas.org/legal/infopolicy.html>

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s herpes or HSV or HSV1 or HSV2

29038 HERPES  
13859 HSV  
2213 HSV1  
477 HSV2  
L1 31321 HERPES OR HSV OR HSV1 OR HSV2

=> s ((acyclovir or gancyclovir or nucleoside)(w)(phosphate or phosphonate)) or PMEA or (phosphonomethoxyethyl adenine) or phosphonomethoxyethyladenine

4492 ACYCLOVIR  
383 GANCYCLOVIR  
52490 NUCLEOSIDE  
624026 PHOSPHATE  
27442 PHOSPHONATE  
778 (ACYCLOVIR OR GANCYCLOVIR OR NUCLEOSIDE) (W) (PHOSPHATE OR PHOSPHONATE)  
488 PMEA  
90 PHOSPHONOMETHOXYETHYL  
62677 ADENINE  
51 PHOSPHONOMETHOXYETHYL ADENINE  
(PHOSPHONOMETHOXYETHYL(W)ADENINE)  
25 PHOSPHONOMETHOXYETHYLADENINE  
L2 1224 ((ACYCLOVIR OR GANCYCLOVIR OR NUCLEOSIDE) (W) (PHOSPHATE OR PHOSPHONATE)) OR PMEA OR (PHOSPHONOMETHOXYETHYL ADENINE) OR PHOSPHONOMETHOXYETHYLADENINE

```
=> s 11 and 12  
L3          102 L1 AND L2  
=> s 13 and (PY<2003 or AY<2003 or PRY<2003)  
    22984005 PY<2003  
    4506202 AY<2003  
    3975570 PRY<2003  
L4          72 L3 AND (PY<2003 OR AY<2003 OR PRY<2003)
```

```
=> file stnguide
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.85	3.73

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FILE 'STNGUIDE' ENTERED AT 14:54:36 ON 28 APR 2009  
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FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Apr 24, 2009 (20090424/UP).
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=> file hcplus  
COST IN U.S. DOLLARS  
          SINCE FILE ENTRY  
          FULL ESTIMATED COST          0.07          3.80
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FILE 'HCPLUS' ENTERED AT 14:55:16 ON 28 APR 2009  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
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FILE COVERS 1907 - 28 Apr 2009 VOL 150 ISS 18  
FILE LAST UPDATED: 27 Apr 2009 (20090427/ED)
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HCPlus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

<http://www.cas.org/legal/infopolicy.html>

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s thymidine kinase
```

57011 THYMIDINE  
348113 KINASE  
L5 10514 THYMIDINE KINASE  
(THYMIDINE (W) KINASE)

=> s 14 and 15

L6 11 L4 AND L5

=> file stnguide

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.85	6.65

FILE 'STNGUIDE' ENTERED AT 14:55:18 ON 28 APR 2009  
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FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Apr 24, 2009 (20090424/UP).

=> d 16 1-11 ti abs bib  
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L6 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Resistance of herpesviruses to antiviral drugs: Clinical impacts and  
molecular mechanisms  
AB A review. Nucleoside analogs such as acyclovir and ganciclovir have been  
the mainstay of therapy for alphaherpesviruses [herpes simplex  
virus (HSV) and varicella-zoster virus (VZV)] and  
cytomegalovirus (CMV) infections, resp. Drug-resistant herpesviruses are  
found relatively frequently in the clinic, almost exclusively among  
severely immunocompromised patients receiving prolonged antiviral therapy.  
For instance, close to 10% of patients with AIDS receiving i.v.  
ganciclovir for 3 mo excrete a drug-resistant CMV isolate in their blood  
or urine and this percentage increases with cumulative drug exposure.  
Many studies have reported that at least some of the drug-resistant  
herpesviruses retain their pathogenicity and can be associated with  
progressive or relapsing disease. Viral mutations conferring resistance  
to nucleoside analogs have been found in either the drug  
activating/phosphorylating genes (HSV or VZV thymidine  
kinase, CMV UL97 kinase) and/or in conserved regions of the viral  
DNA polymerase. Currently available second line agents for the treatment  
of herpesvirus infections—the pyrophosphate analog foscarnet and the  
acyclic nucleoside phosphonate derivative cidofovir—also  
inhibit the viral DNA polymerase but are not dependent on prior  
viral-specific activation. Hence, viral DNA polymerase mutations may lead  
to a variety of drug resistance patterns which are not totally predictable  
at the moment due to insufficient information on specific drug binding  
sites on the polymerase. Although some CMV and HSV DNA  
polymerase mutants have been found to replicate less efficiently in cell  
cultures, further research is needed to correlate viral fitness and clin.  
outcome.  
AN 2002:856088 HCAPLUS <<LOGINID::20090428>>  
DN 138:2047  
TI Resistance of herpesviruses to antiviral drugs: Clinical impacts and  
molecular mechanisms

AU Gilbert, Christian; Bestman-Smith, Julie; Boivin, Guy  
CS Research Center in Infectious Diseases, Centre Hospitalier Universitaire  
de Quebec and Laval University, Quebec City, QC, Can.  
SO Drug Resistance Updates (2002), 5(2), 88-114  
CODEN: DRUPFW; ISSN: 1368-7646  
PB Elsevier Science Ltd.  
DT Journal; General Review  
LA English  
RE.CNT 197 THERE ARE 197 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2009 ACS on STN  
TI Design, Synthesis, and Biological Evaluation of Novel Nucleoside and  
Nucleotide Analogues as Agents against DNA Viruses and/or Retroviruses  
GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A novel strategy was developed for the synthesis of N7-purine acyclic nucleosides. The key step involved the reaction between [2-(p-methoxyphenoxy)ethoxy]methyl chloride and N9-tritylated nucleobases followed by concomitant self-detritylation. The N7-guanine acyclic nucleoside exhibited antiviral activity, but was phosphorylated by both HSV and Vero cell thymidine kinases; thus, it showed more potent cellular toxicity than acyclovir. The N7-adenine acyclic nucleoside was found to be an excellent antiviral agent as well as a good inhibitor of calf mucosal adenosine deaminase. This inhibitory property allows for a greater expression of antiviral activity of antiviral agents, such as N9-adenine acyclic nucleoside and ara-A. The N7-adenine acyclic nucleoside was phosphorylated neither by herpes simplex virus (HSV) thymidine kinase nor by Vero cell thymidine kinase, yet it enhanced the rate constant for the monophosphorylation of acyclovir by HSV thymidine kinase. Consequently, the combination of acyclovir and N7-adenine acyclic nucleoside exhibited greater antiviral activity than acyclovir alone. 7-[2-(Phosphonomethoxy)ethyl]adenine was also synthesized. The key step involved the reaction of 9-(2-cyanoethyl)adenine with Me iodoacetate in the presence of lithium 2,2,6,6-tetramethylpiperidine in THF. Unlike 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), the N7-isomer was not phosphorylated effectively by 5-phosphoribosyl 1-pyrophosphate synthetase (PRPP synthetase); thus, it did not exhibit pronounced antiviral activity. An adenine dinucleotide 5'-monophosphate I and its butenolide ester were also synthesized. Compound I showed substrate activity toward PRPP synthetase and exhibited notable activity against DNA viruses. The antiviral activity of the butenolide ester derivative was found to be higher than that of the parent mol. Compound I is susceptible to degradation by snake venom and spleen phosphodiesterases. However, its resp. butenolide ester derivative was completely resistant to snake venom and spleen enzymes. Guanine and adenine butenolide ester derivs. II (R1 = NH<sub>2</sub>, R2 = H; R1 = OH, R2 = NH<sub>2</sub>) were also synthesized and exhibited notable anti-DNA virus and anti-retrovirus activity in vitro. Final compds. were evaluated for their inhibitory effect on HSV-1-induced mortality in NMRI mice. The N7-adenine acyclic nucleoside [LD50 (i.p.) 950 mg/kg], the butenolide ester of I [LD50 (i.p.) 675 mg/kg], and II (R1 = NH<sub>2</sub>, R2 = H) [LD50 (i.p.) 710 mg/kg] were found to be potent anti-HSV-1 agents in vivo. In addition, II (R1 = NH<sub>2</sub>, R2 = H) efficiently decreased tumor formation induced by Moloney murine sarcoma virus (MSV) in NMRI mice while significantly increasing the survival time of MSV-infected mice.

AN 2001:677297 HCPLUS <<LOGINID::20090428>>  
DN 135:371947  
TI Design, Synthesis, and Biological Evaluation of Novel Nucleoside and  
Nucleotide Analogues as Agents against DNA Viruses and/or Retroviruses  
AU Hakimelahi, Gholam Hossein; Ly, Tai Wei; Moosavi-Movahedi, Ali A.; Jain,  
Moti L.; Zakerinia, Maryam; Davari, Hady; Mei, Hui-Ching; Sambaiah, Thota;  
Moshfegh, Ali A.; Hakimelahi, Shahram  
CS Institute of Chemistry, Academia Sinica, Taipei, 115, Taiwan  
SO Journal of Medicinal Chemistry (2001), 44(22), 3710-3720  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
OS CASREACT 135:371947  
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Antiviral drugs against herpes infections  
AB A review with 34 refs. Several new and promising antiviral drugs have  
been approved which allow better options to control infections caused by  
herpes virus. Vidarabine has been the earliest available drug  
against herpes simplex (HSV) and varicella zoster  
(VZV), but is an agent that is rarely used at present. Acyclovir has  
replaced vidarabine in treating herpes infections in  
immunocompetent and immuno compromised patients. The low oral  
bioavailability of acyclovir, as well as emergence of drug resistant  
strains have stimulated efforts towards development of newer compds. for  
treatment of herpes infection. These include penciclovir and  
its oral prodrug famciclovir and the oral prodrug form of acyclovir,  
valacyclovir. These drugs are dependent on virus encoded  
thymidine kinase (TK) for their intracellular activation  
(phosphorylation) and, upon conversion to their triphosphate form which  
act as inhibitors/alternative substrate of viral DNA polymerase.  
Therefore resistance of these drugs may occur for virus mutants that are  
TK-deficient. Newer drugs as Sorivudine which is a nucleoside analog has  
been pursued in treating herpes infections. Foscarnet, which  
does not require any previous metabolism to interact with viral DNA polymerase  
is useful in clin. settings when TK deficient mutant strains emerge.  
Cidofovir, an acyclic nucleoside phosphonate is yet  
another available drug to which TK deficient strains are sensitive. This  
review describes these currently available antiviral drugs against  
herpes virus, some approved and others under clin. evaluation for  
approval.

AN 2001:48798 HCPLUS <<LOGINID::20090428>>  
DN 135:131486  
TI Antiviral drugs against herpes infections  
AU Vajpayee, Madhu; Malhotra, Neena  
CS Department of Microbiology, All India Institute of Medical Sciences, New  
Delhi, 110 029, India  
SO Indian Journal of Pharmacology (2000), 32(6), 330-338  
CODEN: INJPD2; ISSN: 0253-7613  
PB Indian Pharmacological Society  
DT Journal; General Review  
LA English  
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Hydroxyurea potentiates the antiherpesvirus activities of purine and  
pyrimidine nucleoside and nucleoside phosphonate

analog

AB Hydroxyurea has been shown to potentiate the anti-human immunodeficiency virus activities of 2',3'-dideoxynucleoside analogs such as didanosine. We have now evaluated in vitro the effect of hydroxyurea on the antiherpesvirus activities of several nucleoside analogs (acyclovir [ACV], ganciclovir [GCV], penciclovir [PCV], lobucavir [LBV], (R)-9-(4-hydroxy-2-(hydroxymethyl)butyl)guanine [H2G], and brivudin and nucleoside phosphonate analogs (cidofovir [CDV] and adefovir [ADV]). When evaluated in cytopathic effect (CPE) reduction assays, hydroxyurea by itself had little effect on CPE progression and potentiated in a subsynergistic (herpes simplex virus type 1 [HSV-1]) to synergistic (HSV-2) fashion the antiviral activities of ACV, GCV, PCV, LBV, H2G, ADV, and CDV. Hydroxyurea also caused marked increases in the activities of ACV, GCV, PCV, LBV, and H2G (compds. that depend for their activation on a virus-encoded thymidine kinase [TK]) against TK-deficient (TK-) HSV-1. In fact, in combination with hydroxyurea the 50% effective concns. of these compds. for inhibition of TK- HSV-1-induced CPE decreased from values of 20 to  $\geq$ 100  $\mu$ g/mL (in the absence of hydroxyurea) to values of 1 to 5  $\mu$ g/mL (in the presence of hydroxyurea at 25 to 100  $\mu$ g/mL). When evaluated in a single-cycle virus yield reduction assay, hydroxyurea at a concentration of 100  $\mu$ g/mL inhibited progeny virus production by 60 to 90% but had

little effect on virus yield at a concentration of 25  $\mu$ g/mL. Under these assay conditions hydroxyurea still elicited a marked potentiating effect on the antiherpesvirus activities of GCV and CDV, but this effect was less pronounced than that in the CPE reduction assay. It is conceivable that the potentiating effect of hydroxyurea stems from a depletion of the intracellular deoxynucleoside triphosphate pools, thus favoring the triphosphates of the nucleoside analogs (or the diphosphates of the nucleoside phosphonate analogs) in their competition with the natural nucleotides at the viral DNA polymerase level. The possible clin. implications of these findings are discussed.

AN 1999:784932 HCPLUS <<LOGINID::20090428>>

DN 132:117100

TI Hydroxyurea potentiates the antiherpesvirus activities of purine and pyrimidine nucleoside and nucleoside phosphonate analogs

AU Neyts, J.; De Clercq, E.

CS Rega Institute for Medical Research, Louvain, B-3000, Belg.

SO Antimicrobial Agents and Chemotherapy (1999), 43(12), 2885-2892

CODEN: AMACQ; ISSN: 0066-4804

PB American Society for Microbiology

DT Journal

LA English

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN

TI Nucleoside analog phosphates for topical use in the treatment of herpes virus infections

AB Compns. for topical use in herpes virus infections comprise anti-herpes nucleoside analog phosphate esters, e.g. acyclovir monophosphate, acyclovir diphosphate, and acyclovir triphosphate which show increased activity against native strains of herpes virus as well as against resistant strains, particularly thymidine kinase neg. strains of virus. Also disclosed are methods for treatment of herpes infections with nucleoside phosphates. Anti-herpes nucleoside analogs phosphate esters include the phosphoramidates and phosphothiorates, as well as polyphosphates comprising C and S bridging atoms.

AN 1999:175589 HCAPLUS <<LOGINID::20090428>>  
 DN 130:218263  
 TI Nucleoside analog phosphates for topical use in the treatment of  
 herpes virus infections  
 IN Hostetler, Karl Y.  
 PA USA  
 SO U.S., 19 pp., Cont.-in-part of U.S. 5,580,571.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5879700	A	19990309	US 1995-480456	19950607 <--
	US 5580571	A	19961203	US 1993-60258	19930512 <--
	CA 2222154	A1	19961219	CA 1996-2222154	19960606 <--
	WO 9640088	A1	19961219	WO 1996-US10085	19960606 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU	9663842	A	19961230	AU 1996-63842	19960606 <--
EP	831794	A1	19980401	EP 1996-923289	19960606 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1192138	A	19980902	CN 1996-195922	19960606 <--
	JP 11507642	T	19990706	JP 1997-502194	19960606 <--
	CN 1221609	A	19990707	CN 1998-123863	19981030 <--
PRAI	US 1991-777683	B2	19911015	<--	
	US 1993-60258	A2	19930512	<--	
	US 1995-480456	A	19950607	<--	
	WO 1996-US10085	W	19960606	<--	

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2009 ACS on STN  
 TI Acyclovir derivatives for topical use  
 AB The invention involves compns. for topical use in herpes virus  
 infections comprising anti-herpes nucleoside analog phosphate  
 esters, such as acyclovir monophosphate, acyclovir diphosphate, and  
 acyclovir triphosphate, which show increased activity against native  
 strains of herpes virus as well as against resistant strains,  
 particularly thymidine kinase neg. strains of virus.  
 Anti-herpes nucleoside analogs phosphate esters include the  
 phosphoramidates and phosphothioriates, as well as polyphosphates  
 comprising C and S bridging atoms.

AN 1997:121416 HCAPLUS <<LOGINID::20090428>>  
 DN 126:135594

OREF 126:26139a,26142a

TI Acyclovir derivatives for topical use

IN Hostetler, Karl Y.

PA Hostetler, Karl Y., USA

SO PCT Int. Appl., 34 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 9640088 A1 19961219 WO 1996-US10085 19960606 <--  
 W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,  
 ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,  
 LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,  
 SE, SG  
 RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,  
 IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN  
 US 5879700 A 19990309 US 1995-480456 19950607 <--  
 AU 9663842 A 19961230 AU 1996-63842 19960606 <--  
 EP 831794 A1 19980401 EP 1996-923289 19960606 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, FI  
 JP 11507642 T 19990706 JP 1997-502194 19960606 <--  
 PRAI US 1995-480456 A 19950607 <--  
 US 1991-777683 B2 19911015 <--  
 US 1993-60258 A2 19930512 <--  
 WO 1996-US10085 W 19960606 <--  
 RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
 TI Nucleoside analogs for topical use in herpesvirus infections  
 AB Comps. for topical use in herpesvirus infections comprise anti-  
 herpes nucleoside analog phosphate esters, such as acyclovir  
 monophosphate and acyclovir diphosphate, which show increased activity  
 against native strains of herpesvirus as well as against resistant  
 strains, particularly thymidine kinase-neg. strains of  
 the virus. Thus, acyclovir monophosphate was more effective than  
 acyclovir in treatment of lesions in mice infected with an  
 acyclovir-resistant strain of herpes simplex virus type 1.  
 Acyclovir monophosphate was prepared by reaction of acyclovir with POC13 in  
 P(O)(OMe)3 followed by neutralization with aqueous NaOH.  
 AN 1996:754377 HCPLUS <>LOGINID::20090428>>  
 DN 126:70124  
 OREF 126:13441a,13444a  
 TI Nucleoside analogs for topical use in herpesvirus infections  
 IN Hostetler, Karl Y.  
 PA Hostetler, Karl Y., USA  
 SO U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 777,683, abandoned.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5580571	A	19961203	US 1993-60258	19930512 <--
US 5654286	A	19970805	US 1995-480525	19950607 <--
US 5879700	A	19990309	US 1995-480456	19950607 <--
US 5756116	A	19980526	US 1996-758501	19961202 <--
US 6015573	A	20000118	US 1997-991740	19971216 <--
PRAI US 1991-777683	B2	19911015	<--	
US 1993-60258	A2	19930512	<--	
US 1996-758501	A1	19961202	<--	

OS CASREACT 126:70124  
 RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
 TI Phenotypic resistance of herpes simplex virus type 1 strains  
 selected in vitro with antiviral compounds and combinations thereof  
 AB Several drug resistant herpes simplex virus type 1 (HSV)

-1) strains were obtained under the selective pressure of various antiherpetic drugs used alone or in combination. Their susceptibility to a wide range of antiviral compds. was determined. Strains selected under the pressure of brivudine (BVDU) or 1- $\beta$ -D-arabinofuranosyl-(E)-5-(2-bromovinyl)uracil (BVaraU) alone were composed of two virus populations: (1) virus resistant to BVDU and BVaraU but not to acyclovir (ACV) or ganciclovir (GCV), which is suggestive of an alteration in the thymidylate kinase activity associated with viral thymidine kinase (TK) (responsible for the phosphorylation of BVDU-monophosphate to BVDU-diphosphate); and (2) virus resistant to TK-dependent drugs (i.e. ACV, GCV, BVDU and BVaraU) as well as double-mutant strains with decreased sensitivity to both TK-dependent compds. and the pyrophosphate analogs foscarnet (PFA) and phosphonoacetic acid (PAA) (suggestive of mutations at the level of the DNA polymerase) were recovered under the selective pressure of ACV alone or in combination with BVDU or BVaraU. Combinations of BVDU or BVaraU with PFA or PAA led to strains resistant only to BVDU and BVaraU or double-mutant strains resistant to BVDU, BVaraU and the pyrophosphate analogs, but not to strains resistant to other TK-dependent drugs. Interestingly, strains resistant to ACV, BVDU, GCV and/or the pyrophosphate analogs PFA and PAA remained sensitive to the (S)-3-hydroxy-2-phosphonyl-methoxypropyl (HPMP) derivs. of cytosine (HPMPC) and adenine (HPMPA).

AN 1996:594451 HCAPLUS <<LOGINID::20090428>>

DN 125:292318

OREF 125:54375a, 54378a

TI Phenotypic resistance of herpes simplex virus type 1 strains selected in vitro with antiviral compounds and combinations thereof

AU Morfin, F.; Snoeck, R.; Andrei, G.; De Clercq, E.

CS Rega Inst. Med. Res., Katholieke Universiteit Leuven, Louvain, B-3000, Belg.

SO Antiviral Chemistry & Chemotherapy (1996), 7(5), 270-275

CODEN: ACCHEH; ISSN: 0956-3202

PB Blackwell

DT Journal

LA English

L6 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2009 ACS on STN

TI Acyclic nucleosides as antiviral compounds

AB A review with 94 refs. Acyclovir is an effective drug for the treatment of HSV and VZV infections, which after phosphorylation to the triphosphate, inhibits viral DNA polymerase. Acyclovir has low oral bioavailability, therefore prodrugs have been developed, and the L-valyl ester, valaciclovir, recently has been licensed for the treatment of shingles. Ganciclovir is used against CMV, and famciclovir, a lipophilic prodrug of penciclovir, is marketed for shingles. The acyclic nucleoside phosphonates are active against thymidine kinase -resistant viral strains. Promising analogs are PMEA (in clin. trial for the treatment of AIDS) and (S)-HPMPC (good in vivo activity against HSV, VZV, CMV, and EBV). Oligonucleotides incorporating acyclic nucleosides at the 3'- and 5'-ends, or constituted of amino acyclic nucleosides, are resistant to cleavage by nucleases and may be useful in antisense and/or antigenic therapy. HEPT is active against HIV-1. It binds in a hydrophobic pocket on reverse transcriptase, rather than in the polymerase active site. Some acyclic nucleosides are potent inhibitors of purine and pyrimidine nucleoside phosphorylase. These compds. may have a therapeutic niche in combination therapy with antiviral and anticancer nucleosides, and in the treatment of diseases involving the T-cell.

AN 1996:420923 HCAPLUS <<LOGINID::20090428>>

DN 125:75098

OREF 125:14003a, 14006a

TI Acyclic nucleosides as antiviral compounds  
AU Freeman, Sally; Gardiner, John M.  
CS Department Pharmacy, University Manchester, Manchester, M139PL, UK  
SO Molecular Biotechnology (1996), 5(2), 125-137  
CODEN: MLBOEO; ISSN: 1073-6085  
PB Humana  
DT Journal; General Review  
LA English

L6 ANSWER 10 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Inhibitors of bovine herpes mammillitis virus infections in cultured cells and in vaginally infected guinea pigs  
AB Bovine herpes mammillitis virus or bovine herpesvirus type 2 (BHV-2) causes ulcerative lesions on the teats and udders of infected cows. The authors investigated several nucleoside and nucleotide analogs as potential BHV-2 inhibitors. These included acyclovir, ganciclovir, 5-iodo-2'-deoxyuridine (IUdR), 1-(2'-deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl) derivs. of 5-iodocytosine (FIAC), 5-iodouracil (FIAU), and 5-methyluracil (FMAU), and various 3-hydroxyphosphonylmethoxypropyl (HPMP) and 2-phosphonylmethoxyethyl (PME) derivs. of adenine (A), guanine (G), 2,6-diaminopurine (DAP), and/or cytosine (C). Of these, FIAU and FMAU were the most potent in cell culture, inhibiting 50% of BHV-2 plaques at <0.05  $\mu$ M. HPMPA and HPMPG were active at 0.3  $\mu$ M; FIAC, IUdR, and HPMPC at 1.3-2.3  $\mu$ M; PMEDAP and ganciclovir at 20-25  $\mu$ M; acyclovir and PMEA at >100  $\mu$ M. The two most potent agents, FIAU and FMAU, inhibited uninfected embryonic bovine tracheal cell growth by 50% at >100  $\mu$ M and 53  $\mu$ M, resp., resulting in selectivity indexes (ratio of the 50% inhibitory concentration for cell growth to the 50% inhibitory concentration for plaque formation) of >2200 and 1100. Greater degrees of antiviral activity and selectivity were obtained in infected guinea pig embryo cells treated with FIAU, FMAU, and HPMPC. Infected cell exts. containing BHV-2-induced thymidine kinase activity phosphorylated FIAU, FMAU, and IUdR at nearly the same rate as thymidine, whereas FIAC, acyclovir, and ganciclovir were phosphorylated at  $\leq$ 5% the rate of thymidine. Phosphorylation by this enzyme is required to generate the antivirally active nucleoside triphosphate in infected cells. In guinea pigs infected intravaginally with BHV-2, FMAU treatments of 1, 3.2, and 10 mg kg<sup>-1</sup> per day for 5 days starting 1 day after virus challenge reduced vaginal lesion scores and virus titers in a dose-dependent manner. FIAU (10  $\mu$ M) was as effective as 1  $\mu$ M FMAU by the same regimen. A single treatment with 10  $\mu$ M HPMPC was as active as daily treatments with 3.2 mg FMAU kg<sup>-1</sup>. These results indicate the potential of using antiviral agents to treat bovine herpes mammillitis virus infections in cattle, and the application of guinea pigs to study BHV-2 disease.  
AN 1994:671329 HCPLUS <>LOGINID::20090428>>  
DN 121:271329  
OREF 121:49243a,49246a  
TI Inhibitors of bovine herpes mammillitis virus infections in cultured cells and in vaginally infected guinea pigs  
AU Smee, D. F.; Leonhardt, J. A.; Sugiyama, S. T.; Holy, A.  
CS Inst. Antiviral Res., Utah State Univ., Logan, UT, 84322-5600, USA  
SO Antiviral Chemistry & Chemotherapy (1994), 5(4), 201-8  
CODEN: ACCHEH; ISSN: 0956-3202  
DT Journal  
LA English

L6 ANSWER 11 OF 11 HCPLUS COPYRIGHT 2009 ACS on STN  
TI Properties of a 9-(2-phosphonylmethoxyethyl)adenine (PMEA)-resistant herpes simplex virus type 1 virus mutant  
AB After repeated passages of herpes simplex type 1 (HSV

-1) KOS virus in the presence of 9-(2-phosphonylmethoxyethyl)adenine (PMEA), a mutant denoted PMEAr HSV-1 was isolated which grew well in the presence of 50-100 µg/mL of the drug. PMEAr HSV-1 was still sensitive to the related phosphonate analog (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA). In fact, it was more susceptible to the action of HPMPA than the original virus. PMEAr HSV-1 also retained sensitivity to 5-bromo-2'-deoxyuridine and other, viral thymidine kinase-dependent substances such as (E)-5-(2-bromovinyl)-2'-deoxyuridine. However, PMEAr HSV-1 was much less sensitive to acyclovir, 1-(β-D-arabinofuranosyl)cytosine and 1-(β-D-arabinofuranosyl)thymine than the parental KOS virus.

AN 1990:627872 HCAPLUS <<LOGINID::20090428>>

DN 113:227872

OREF 113:38365a,38368a

TI Properties of a 9-(2-phosphonylmethoxyethyl)adenine (PMEA)-resistant herpes simplex virus type 1 virus mutant

AU Vonda, Vladimir; Anisimova, Emma; Cerny, Jaroslav; Holy, Antonin; Rosenberg, Ivan; Votruba, Ivan

CS Dep. Exp. Virol., Inst. Sera Vaccines, Prague, 101 03, Czech.

SO Antiviral Research (1990), 14(2), 117-21

CODEN: ARSRDR; ISSN: 0166-3542

DT Journal

LA English